IN CONCLUSION

We all know that there are various infections, such as syphilis, leprosy, glanders, rhinoscleroma, infected foreign bodies, and some forms of malignancy or new growth, that may produce lesions that look like tuberculosis. Also, the microscopic picture of these lesions may look like tuberculosis. These conditions must, of course, be eliminated in any differential diagnosis of a chronic nonhealing lesion of the nose. These other causes have been fully discussed at meetings and in the literature in recent years.

However, as the relationship of sarcoid to tuberculosis has not been discussed at our meetings, I felt that it would be worth while to limit my discussion to this subject. It is my belief that sarcoid is not a separate disease, but should be considered as a phase of tuberculosis.

490 Post Street.

IMMUNITY: CLINICAL AND EXPERIMENTAL OBSERVATIONS*

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IMMUNITY is the topic of conversation by lay people almost as commonly as is the weather. At any bridge or tea will be heard such remarks as, "Johnny is just like his father; he catches everything that comes along. He has had measles three times. Susan never gets anything," etc. Many such popular beliefs, though not all, are supported by clinical observation; but when an attempt is made to measure immunity it remains one of the most intangible problems of science.

A cross section of a sample of the population at any age level should show a considerable variation in different individuals' ability to combat disease. Also a longitudinal study of any one person from birth to death should show a change in his resistance to infection or to any given infection at different times.

Even at birth may be revealed considerable variations in individuals' immune mechanism. At a delivery everyone is aware of the tension with which is awaited the first cry, indicating the establishment of respiration and circulation in the detached infant. The newborn has made a happy landing—so we think. There are, however, other functions than breathing and circulation which must become established, and one of these is the ability to live in an unsterile environment. Occasionally an infant in the nursery, even with normal heart and lungs, develops a breast abscess or pyelitis or even septicemia or meningitis. Frequently the causative organism is the ordinary staphylococcus or B. coli. A good doctor does, and rightly should, look for the source of infection in the environment—faulty technique, contamination of food, infection in an attendant, etc.—but in most instances he looks in vain, for the fault probably is within the baby himself. Some infants undoubtedly are inherently incapable of surviving bacterial invasion. Their bodies behave more like a culture medium than a living organism mobilizing to combat an invader. These babies simply turn sour and die.

If the newborn period is survived uneventfully, differences may manifest themselves later. A few years back a child died in our ward of measles encephalitis. The history of the boy brought out the interesting fact that he had had measles a few years previously. Second attacks of this disease are very unusual, and physicians of long experience will report only its rare occurrence. In this instance there was no reason to doubt the diagnosis because the same doctor had seen the child with both attacks, and in his records of the first was noted the presence of Koplik spots. Furthermore, the child had been vaccinated twice within a period of a few years, with a take each time. This, too, is unusual. He probably was a child with a defective immunizing mechanism. It is surprising he survived to childhood. At any age-level such differences manifest themselves. They should be less apparent later in life because of the toll along the way. Although modern care and precautions will safeguard many to later periods, yet the chances are great that some infection will catch up with them before they have traveled very far into time.

The longitudinal study of the individual is equally fascinating. Whether he has a good or poor resistance, his own reactions to a given infection may change. Thus, during the first few months of life he is immune to measles; this period is followed by increased susceptibility during the next year or two, and then during childhood the disease, if contracted, is not unduly severe. One attack confers immunity. In contrast to this, erysipelas, untreated, has a mortality of nearly 100 per cent in the newborn period. After that children withstand erysipelas well, and only in adult life, particularly old age, again is it a severe disease. It confers no lasting immunity.

To some infections the normal response is permanent immunity. This is true of chicken-pox, smallpox, measles, mumps, scarlet fever, and a number of other diseases. However, permanent immunity to the first infection of even these diseases is only relative. As pointed out earlier, authentic cases of second attacks of measles and chicken-pox are rare, but of whooping cough and scarlet fever are not uncommon. Within the last few years reinfections in poliomyelitis have been reported and ancient manuscripts record second attacks of smallpox. In other types of infection, such as tonsillitis, immunity is established gradually after repeated infections; attacks are frequent in childhood and gradually decrease with age. Other infections may make the individual more instead of less susceptible to repeated exposures. This appears to be the case with erysipelas and influenza. Still other organisms, notably the tubercle bacillus, produce entirely different manifestations in primary and secondary invasions. This latter characteristic has not been studied carefully in other diseases. It is possible that it manifests itself in rheumatic fever, nephritis, and others.

Immunity is not only intangible, it is at times capricious. Occasionally an individual is found

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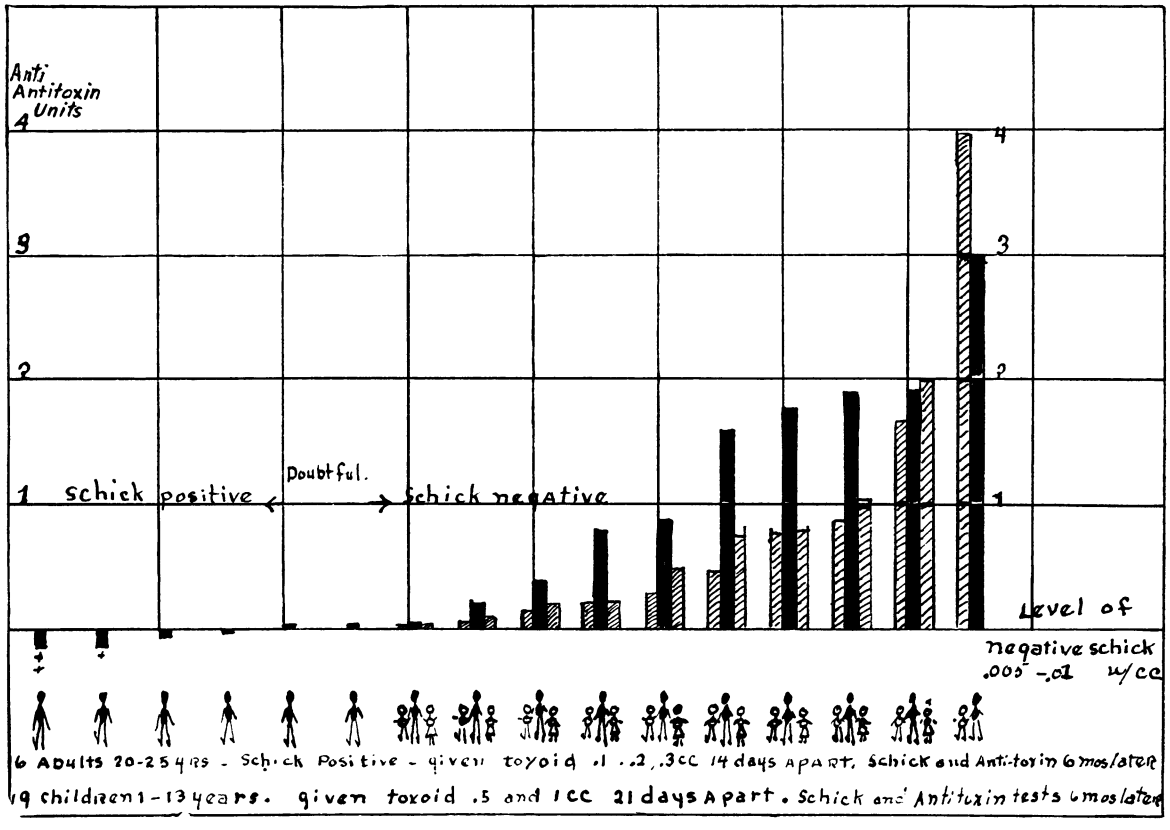

Chart 1.—Variations in serum antitoxin six months after immunization.

whose immune mechanism can best be described as going into reverse. Thus, a young man "hyper-immunized" to the hemolytic streptococcus, when exposed to scarlet fever in the course of his work developed a very bizarre form of the disease. He had pneumonia, thyroiditis, multiple soft tissue abscesses, and jaundice. He appeared to be sensitized to the organism instead of immunized.

At other times a person's immune mechanism appears to be completely paralyzed. As an example, a baby given an overdose of codein by mistake developed a streptococcic meningitis. Direct examination of the spinal fluid looked like a cultural growth; there were practically no white blood cells and the organisms appeared in chains of eight or ten cocci. Other peculiar phenomena occur, such as the sudden invasion of the body with the Staphylococcus aureaus or albus. The portal of entry may be an insignificant scratch or blister. Whether an accident of this type is due to a suppression of immunity or a synergistic action of two or more organisms or some totally unexplained phenomenon is not known.

One of the most sporting studies in science has been the attempt to establish immunity by artificial means. A milk-maid's remark about cow-pox started Jenner on the path which led to immunization against smallpox by vaccination. Toxoid in the prevention of diphtheria, although lacking as romantic a beginning, has an equally fascinating history. These two discoveries remain the brilliant examples of successful artificial immunization. Others are in use with varying degrees of success.

There is probably no bodily function that lends itself so poorly to accurate investigation as immunity. We know, for instance, that the serum of an individual who has recovered from measles has protective substances in it that, if given in certain dosage early after exposure, will protect the recipient against the disease. This property does not lend itself to any accurate measurements.

The only substance which can be studied with any degree of accuracy is the diphtheria antitoxin content of serum. Various methods, all similar, have been used, but the technique perfected by Claus Jensen of the Serum Institute in Copenhagen is the easiest and most accurate and, therefore, has been generally accepted. Dr. Mary Schmeckebier has used, with some modifications, this technique in our laboratory. The shaved and depilated rabbit's back and sides are used for the determinations. A standard toxin, treated with a standard antitoxin in various dilutions, is used as a control on each rabbit. The control is paralleled by the standard toxin in the same amounts treated with various dilutions of the serum of unknown antitoxin content. The neutralization point is readily determined and the units or fraction of unit per cubic centimeter can be computed. Reactions can be read accurately down to 1/2500 of a unit.

With the use of this technique many interesting studies have been made. The absorption curve of antitoxin when administered for diphtheria, as well as the rate of disappearance of it, have been determined by Madsen. Jensen made many studies on antitoxin production and elimination after toxoid injections.

The purpose of this paper, however, is to show that a study of antitoxin in human serum supports for this one content our theory of individual variations.

In Chart 1 the plottings represent two groups, one of nineteen children, one to thirteen years, in whom antitoxin determinations were made six months after two doses of toxoid one-half and one cubic centimeter each, twenty-one days apart, had been given; and one of sixteen medical students, twenty-two to twenty-five years of age. This latter group were Schick-positive originally, then immunized with three doses of toxoid, 0.1, 0.2, and 0.3 cubic centimeter fourteen days apart. The antitoxin determinations and Schick tests were done six months after the immunizations. The children were all Schick-negative, but varied in antitoxin content from 1/25 to 4 units per cubic centimeter. Among the adults were four positive and twelve negative reactors with variations in antitoxin from less than 1/250 to 3 units per cubic centimeter. This latter group, having been chosen on the basis of a positive Schick, were more select than the children not so chosen. The level at which our skin tests were negative was between 1/200 and 1/100 unit. This figure is lower than the original of 1/30 unit per cubic centimeter, but is the level most other recent workers have found for a negative Schick. Some Schick-positive adults are very resistant to immunization, and interesting observations on them have been made, but that study is beyond the scope of this paper.

A longitudinal study of several individuals has been started. Determinations have been made at intervals throughout the past year. When the figures are plotted the curves tend to rise through the winter and spring months.

This rise, however, is not constant, but broken by many fluctuations. The cause of these fluctuations is not known. One reason for making this type of study of individuals was the hope that by repeated tests at short intervals we might be fortunate enough to pick up any sudden change in the amount of neutralizing substances, should such a change occur. There are many popular beliefs and considerable scientific literature on the subject of the effect of endocrines, vitamins, fatigue, illness, etc., on immunity. Even if changes occur, it obviously will be extremely difficult to interpret them without a vast amount of material. The field has unlimited problems for future exploration. Experimental evidence, however, does support the clinical observations that immunity is fluctuating and not static. Variations occur both in a cross section of the population and in a longitudinal study of individuals.

This method of studying immunity is crude. It measures rather roughly the neutralizing properties of serum for diphtheria toxin, but tells us nothing of the character of this substance or substances and nothing of cell immunity. Both the serum and cells are complicated structures which in physics and chemistry can be broken down into molecules, atoms, protons, etc. Each is a system as spacious in its own little self as is the solar system to us. Where in this structure then is immunity? The patient can be bled and the immune properties are restored to the blood; cells are replaced after wear and tear by new ones that possess the same property. And yet, as noted above, immunity, as we know it, may suddenly disappear. To those who like to chase rainbows this intangible and capricious factor of life remains a fascinating subject.

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IDIOPATHIC ULCERATIVE COLITIS: THE EFFECTIVENESS OF LIVER EXTRACT IN ITS TREATMENT*

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DESPITE an intense interest in idiopathic ulcerative colitis, the etiology of this condition remains unknown. Consequently, the effectiveness of any form of treatment must be judged from clinical observation rather than scientific experimentation. In presenting a new form of treatment it is not only important to give the results obtained by this treatment, but also to review the probable causes of the disease and their theoretical relationship to the mode of therapy applied.

ETIOLOGY OF COLITIS: CURRENT VIEWS

At present the majority of the investigators studying ulcerative colitis believe it is primarily due to an infection involving the bowel mucosa. Evidence in favor of this has frequently been presented by Bargen of the Mayo Clinic. No specific organism has been agreed upon, and vaccine and serum therapy have been most disappointing. In the past the cause has been vaguely designated as "diminished resistance" of the colon to infection, and recently Felsen [1] has emphasized that a previous attack of bacillary dysentery may make the bowel wall more susceptible to bacterial invasion. Diet and vitamine therapy, based on the lowered resistance hypothesis, have been equally disappointing. That some cases may be due to food allergy is now well recognized; but it is a rare case indeed in which the removal of some type of protein from the diet will produce a cure or even a satisfactory remission. An important and little-understood factor in causing ulcerative colitis is the effect of nervous-system influences on the activity of the colon. Nervous, highstrung patients may develop their attacks coincident with shock, great fatigue or prolonged nervous tension, and may develop remissions on sedative therapy alone. The effects of these four factors on the colon have been schematically presented in Figure 1. It is important to appreciate that one or more of these factors may contribute to the illness of any given patient, and that all of them must be considered in each individual.

LIVER THERAPY: RELATION TO ETIOLOGIC FACTORS

In what way could any beneficial effect of liver therapy be correlated with these etiologic factors?

* Read before the Section on General Medicine of the California Medical Association at the sixty-eighth annual session, Del Monte, May 1–4, 1939.